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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,108	01/15/2002	Stein Ove Doskeland	Q-64374	8288

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EXAMINER	
YANG, NELSON C	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,108	DOSKELAND ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claims 2-14 is acknowledged and has been entered.

2. Applicant's cancellation of claims 1, 15-20 is acknowledged and has been entered.

3. Applicant's addition of claims 21-29 is acknowledged and has been entered.

4. Claims 2-14, 21-29 are currently pending.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-14, 21-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 21 and 22 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps that detail how the presence of the second ligand is able to be determined. Applicant may wish to incorporate the limitation of claim 9 in order to overcome this rejection.

8. With respect to claims 21-22, the limitation that "wherein the presence of said second ligand in either the bound fraction or the non-bound fraction is indicative of the presence of said phosphatase targeting toxin in said sample" is ambiguous, as presumably the second ligand would have to be either be in the bound fraction or non-bound fraction, regardless of whether the toxin was in the sample or not.

9. With respect to claims 9-10, it is unclear how the presence of the reporter moiety on the first ligand would aid in the detection of the toxin, as presumably the reporter moiety would always produce the same signal.

10. With respect to claim 29, it is unclear if both the first and second ligand are protein phosphatase enzymes, how the first and second ligands would bind to each other. Further clarification is requested.

11. The remaining claims are indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 22, 2, 3, 5, 6, 8, 9, 13, 14, 24, are rejected under 35 U.S.C. 103(a) as being unpatentable over Holmes [US 5,180,665] in view of Maggio [Maggio, Chapter 3: Enzymes as immunochemical labels, 1980, Enzyme-immunoassay, CRC Press, 54-68].

With respect to claim 22, Holmes teaches a method for quantitatively assaying the presence of DSP toxins such as okadaic acid comprising the steps of preparing a marine extract, fractionating the prepared marine extract and selecting the extract fraction containing the toxin to be assayed, contacting a labeled substrate for protein phosphatase and at least one protein phosphatase to the extract in an assay (column 2, lines 46-61). Holmes does not specify the use of ligands immobilized to a solid support.

Maggio, however, teaches that in order to quantify the amount of analyte present in an enzyme-immunoassay, the extent of reaction of the enzyme-labeled ligand with antibody must be determined, which requires a physical separation of the free and antibody-bound fractions. Maggio further teaches that many of the parameters of a suitable separation technique are shared by bothe enzyme-immunoassays and their analogous radioimmunoassay procedures, and in order to maximize precision and sensitivity, one would like to ensure complete separation of the free and bound fractions, such as by solid phase separation using antibodies to immobilize the antigen (toxin) in an sandwich assay (p. 60-64, part C). Holmes also teaches that without an appropriate separation technique, it is very difficult to conclude with certainty that the enzymatic activity of the protein phosphatase is inhibited by okadaic acid present in the sample (column 3, lines 57-63).

Therefore it would have been obvious in the method of Holmes to use ligands such as antibodies bound to a solid support, in order to ensure complete separation of the free and bound labels, so as to maximize the precision and sensitivity of the method.

14. With respect to claim 2, Holmes teaches that DSP toxins come from dinoflagellates and are accumulated in the midgut glands of bivalves feeding on dinoflagellates (column 1, lines 17-20). (column 1, lines 17-20).

15. With respect to claim 3, Holmes teaches that the toxins include okadaic acid (column 2, lines 46-50).

16. With respect to claim 5, Holmes teaches the presence of toxins such as okadaic acid is quantitatively assayed (column 2, lines 36-50).

17. With respect to claim 6, Holmes teaches the samples comprise prepared marine extracts (column 2, lines 50-52).

18. With respect to claim 8, Holmes teaches the protein phosphatase can be protein phosphatase 2A (column 4, lines 12-20).

19. With respect to claims 9-10, Holmes teaches the labeled substrate comprises a labeled phosphate group (column 4, lines 25-30).

20. With respect to claim 13-14, Maggio teaches the use of agarose bead coupled ligands (p.64, pg.3).

21. With respect to claim 24, Maggio teaches the use of passive absorption to coat the microtiter plates (p.64, pg.3).

22. With respect to claim 26, Holmes et al teach that the amount of toxin present is quantitatively measured by the inhibition of desphosphorylation of the labeled substrate by protein phosphatases (column 2, lines 55-61).

23. Claims 21, 2-5, 10, 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Sikorska et al [US 5,264,556] in view of Holmes [US 5,180,665].

With respect to claim 21, Sikorska et al teach solid-phase bound antibodies, where the solid support can be plastic or magnetic beads (column 6, lines 35-45). Sikorska et al further teach enzyme labeled anti-mouse IgG anti-serum for use in the assays (column 5, lines 55-67, table 1), indirect detection by a second antibody with a label (column 6, lines 40-47). Sikorska et al teach that the assays involving the bound antibodies, comprise competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG fixed to a solid-phase (column 12, example II), where free OA inhibits the binding of anti-idiotypic 1/59 IgG to solid phase bound

6/50 IgG $F(ab')_2$. A peroxidase conjugated goat anti-mouse IgG Fc-fragment-specific antiserum is then added to determine the amount of binding (column 12, lines 50-55). Sikorsa et al do not teach using protein phosphatase enzymes instead of 6/50 IgG $F(ab')_2$.

Holmes teach that okadaic acid can be biologically inactivated by a single methyl esterification and therefore, since procedures involving antibodies give no information on the viable biological activity of a detected toxin, they still require validation by activity-based methods of analysis. Holmes further teaches that protein phosphatases such as PP1/PP2A are also capable of detecting the biological activity of okadaic acid (column 4, lines 55-60), and that PP1/PP2A are not inhibited by classical polyether antibiotics such as nigericin, monensin, maduramycin, or salinomycin, therefore providing useful an addition to increasing the number of techniques for analyzing DSP toxins (column 7, lines 35-48).

Therefore, it would have been obvious in the method of Sikorsa et al to use protein phosphatases instead of 6/50 IgG, as suggested by Holmes, since PP1/PP2A are not inhibited by classical polyether antibiotics such as nigericin, monensin, maduramycin, or salinomycin, therefore providing useful an addition to increasing the number of techniques for analyzing DSP toxins, while also providing information as to the biological activity of the detected toxins.

24. With respect to claims 2-3, Sikorska et al teach that okadaic acid is produced by several types of marine dino-flagellates and accumulates in marine sponges, mussels and scallops (column 1, lines 10-15).

25. With respect to claims 4-5, Sikorska et al teach assays involving the bound antibodies, such as competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG

fixed to a solid-phase (column 12, example II), where free OA inhibits the binding of anti-idiotypic /59 IgG to solid phase bound 6/50 IgG $F(ab')_2$.

26. With respect to claim 8, Holmes teaches the use of protein phosphatases such as PP1 or PP2A (column 4, lines 55-60).

27. With respect to claims 9-10, Sikorska et al teach the use of peroxidase conjugated goat anti-mouse IgG Fc-fragment-specific antiserum (column 12, lines 50-55).

28. With respect to claim 10, Sikorska et al teach enzyme labeled anti-mouse IgG anti-serum for use in the assays (column 5, lines 55-67).

29. With respect to claim 14, the antibodies are bound to plastic or magnetic beads (column 6, lines 35-45).

30. With respect to claims 25-26, Sikorska et al teach the direct detection through the use of a single enzyme label (column 5, lines 64-65), but also teach that in cases where an enzyme label causes a loss of activity, an indirect detection method would be preferable (column 5, lines 66-67).

31. With respect to claim 27, Sikorska et al teach that the assays involving the bound antibodies, comprise competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG fixed to a solid-phase (column 12, example II), where free OA inhibits the binding of anti-idiotypic 1/59 IgG. Therefore the presence of bound anti-idiotypic 1/59 IgG would be indirectly related to the presence of okadaic acid.

32. With respect to claim 28, Sikorska et al teach that the assays involving the bound antibodies, comprise competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG fixed to a solid-phase (column 12, example II), where free OA inhibits the binding of

anti-idiotypic 1/59 IgG. Therefore the presence of unbound anti-idiotypic 1/59 IgG would be directly related to the presence of okadaic acid.

33. Claims 21, 22, 2-14, 25-28, are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuura et al [US 5,525,476] in view of Holmes [US 5,180,665].

With respect to claims 21, 22, Matsuura et al teach an antibody specific for a lipophilic compound or antigen, such as okadaic acid (column 8, lines 47-57), immobilized on a suitable insoluble support and reacting with the antigen in a organic extract in a specific manner (column 5, lines 50-56). Matsuura et al further teach using either a competitive method to detect the lipophilic compound by using a labeled antigen (column 5, lines 60-62, column 6, lines 4-22), or using a noncompetitive method such as a sandwich method, in which an excess amount of a labeled second antibody is used (column 5, lines 63-65). Matsuura et al do not teach using protein phosphatase enzymes instead of antibodies.

Holmes, however, teach that okadaic acid can be biologically inactivated by a single methyl esterification and therefore, since procedures involving antibodies give no information on the viable biological activity of a detected toxin, they still require validation by activity-based methods of analysis. Holmes further teaches that protein phosphatases such as PP1/PP2A are also capable of detecting the biological activity of okadaic acid (column 4, lines 55-60), and that PP1/PP2A are not inhibited by classical polyether antibiotics such as nigericin, monensin, maduramycin, or salinomycin, therefore providing useful an addition to increasing the number of techniques for analyzing DSP toxins (column 7, lines 35-48).

Therefore, it would have been obvious in the method of Matsuura et al to use protein phosphatases instead of antibodies, as suggested by Holmes, since PP1/PP2A are not inhibited

by classical polyether antibiotics such as nigericin, monensin, maduramycin, or salinomycin, therefore providing useful an addition to increasing the number of techniques for analyzing DSP toxins, while also providing information as to the biological activity of the detected toxins.

34. With respect to claim 2, Holmes teaches that DSP toxins come from dinoflagellates and are accumulated in the midgut glands of bivalves feeding on dinoflagellates (column 1, lines 17-20). (column 1, lines 17-20).

35. With respect to claim 3, Matsuura et al teach an antibody specific for a lipophilic compound or antigen, such as okadaic acid (column 8, lines 47-57).

36. With respect to claim 4, Matsuura et al teach that the labeled antigens and the unknown amount of antigens are bound competitively (column 6, lines 15-18).

37. With respect to claim 5, Matsuura et al teach that the amount of bound labeled antigens is measured (column 6, lines 63-67).

38. With respect to claim 6, Matsuura et al teach that the method is used for the immunoassay of toxins in marine products (column 25-31).

39. With respect to claim 7, Matsuura et al teach using a noncompetitive method such as a sandwich method, in which an excess amount of a labeled second antibody is used (column 5, lines 63-65).

40. With respect to claim 8, Holmes teaches the use of protein phosphatases such as PP1 or PP2A (column 4, lines 55-60).

41. With respect to claims 9-10, Matsuura et al teach using a noncompetitive method such as a sandwich method, in which an excess amount of a labeled second antibody is used (column 5, lines 63-65).

42. With respect to claims 11-12, Matsuura et al teach that the labeled antigens and the unknown amount of antigens are bound competitively (column 6, lines 15-18), where the antigens comprise okadaic acid (column 8, lines 47-57). Holmes further teaches that the antigens may be microcystine-LR (column 7, lines 25-35).

43. With respect to claims 13-14, Matsuura et al teach that the support may be latex particles (column 5, lines 55-57).

44. With respect to claim 23, Matsuura et al teach that immobilized ligand was immobilized indirectly by dissolving the ligand in 0.083M borate buffered saline, and then blocking with 250 μL of gelatin solution dissolved in BBS (column 10, lines 55-65).

45. With respect to claims 25-26, Matsuura et al teach that the amount of bound labeled antigens is measured (column 6, lines 63-67), which would determine the amount of bound labeled antigens directly, and the amount of unbound labeled antigens indirectly.

46. With respect to claims 27-28, Matsuura et al teach that the amount of bound labeled antigens is measured (column 6, lines 63-67), which would be inversely related to the presence of the toxin in the sample. Matsuura et al also teach sandwich assays, in which an excess amount of a labeled second antibody is used (column 5, lines 63-65). In this situation the amount of bound labeled antibodies would be directly related to the amount of toxins in the sample.

Response to Arguments

47. Applicant's arguments with respect to claims 2-14 have been considered but are moot in view of the new ground(s) of rejection. The following arguments, however, have been addressed:

48. With respect to applicant's argument that that Holmes teaches an enzymatic assay while Maggio teaches a binding assay, it should be noted that the method of detection in the assay of Maggio involves the measurement of enzyme activity (p.67, part C).

Applicant further argues that there is no suggestion provided by Maggio or Holmes that separating bound and unbound fractions would be beneficial in an enzymatic assay. This argument is not found persuasive, as Holmes teach that without an appropriate separation technique, it is very difficult to conclude with certainty that the enzymatic activity of the protein phosphatase is inhibited by okadaic acid present in the sample (column 3, lines 57-63). Thus, the antibody would allow the separation of okadaic acid from the rest of the sample.

Conclusion

49. No claims are allowed.

50. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

51. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

52. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nelson Yang
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oc/13/05